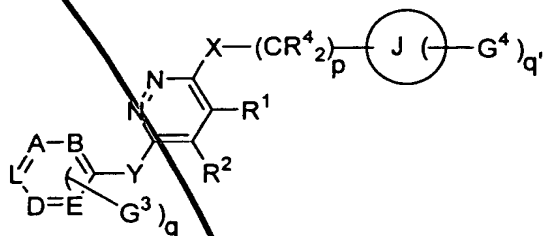


WE CLAIM:

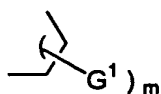
1. A compound having the generalized structural formula



wherein

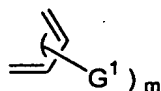
 $R^1$  and  $R^2$  :

- i) independently represent H or lower alkyl;
- ii) together form a bridge of structure



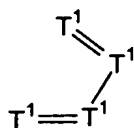
wherein binding is achieved via the terminal carbon atoms;

- iii) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms; or

- iv) together form a bridge of structure



wherein one or two ring members  $T^1$  are N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

 $m$  is 0 or an integer 1 – 4; and $G^1$  is a substituent independently selected from the group consisting of

- $-N(R^6)_2$  ;
- $-NR^3COR^6$  ;

Sub  
A1

5

10

15

20

25

30

- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- phenyl lower alkoxycarbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- halogenated lower alkylthio;

00636519.081000

Sub<sup>5</sup>  
A1

10

15

20

25

- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- -NO<sub>2</sub>;
- -CN;
- amidino;
- guanidino;
- sulfo;
- -B(OH)<sub>2</sub>;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- -OCO<sub>2</sub>R<sup>3</sup>;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- -CHO;
- -OCON(R<sup>6</sup>)<sub>2</sub>;
- -NR<sup>3</sup>CO<sub>2</sub>R<sup>6</sup>;
- -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>

R<sup>3</sup> is H or lower alkyl;

30

R<sup>6</sup> is independently selected from the group consisting of

- H;
- alkyl;

0509030519-031000

- ~~R<sup>4</sup> is H, halogen, or lower alkyl;~~

$p$  is 0, 1, or 2;

X is selected from the group consisting of O, S, and NH;

10

Y is selected from the group consisting of

- $-(\text{CR}^4_2)_n-\text{S}(\text{O})_p-(5\text{-membered heteroaryl})-(\text{CR}^4_2)_s$ ;
- $-(\text{CR}^4_2)_n-\text{C}(\text{G}^2)(\text{R}^4)-(\text{CR}^4_2)_s$ ;

wherein

$n$  and  $s$  are each independently 0 or an integer of  $1-2$ ; and

15

~~G<sup>2</sup> is selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, and -CH<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub>;~~

- $-\text{O}-\text{CH}_2-$  ;
- $-\text{S}(\text{O})-$  ;
- $-\text{S}(\text{O})_2-$  ;
- $-\text{SCH}_2-$  ;
- $-\text{S}(\text{O})\text{CH}_2-$  ;
- $-\text{S}(\text{O})_2\text{CH}_2-$  ;
- $-\text{CH}_2\text{S}(\text{O})-$  ; and
- $-\text{CH}_2\text{S}(\text{O})_2-$

20

25

A and D independently represent N or CH;

B and E independently represent N or CH;

L represents N or CH;

with the provisos that

30

- a) the total number of N atoms in the ring containing A, B, D, E, and L is 1, 2, or 3; and
- b) when L represents CH, at least one of A and D is an N atom;

Sub

5

- 10

15

20

25

30

Sub  
A

- 5

10

- 15

20

25

30

5

10

15

20

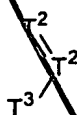
25

30

- lower alkoxy carbonyl-substituted alkylamino;
- phenyl-lower alkoxy carbonyl-substituted alkylamino;
- $-OR^6$ ;
- $-SR^6$ ;
- $-S(O)R^6$ ;
- $-S(O)_2R^6$ ;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- $-OCOR^6$ ;
- $-COR^6$ ;
- $-CO_2R^6$ ;
- $-CON(R^6)_2$ ;
- $-CH_2OR^3$ ;
- $-NO_2$ ;
- $-CN$ ;
- amidino;
- guanidino;
- sulfo;
- $-B(OH)_2$ ;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- $-OCO_2R^3$ ;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p$ (optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p$ (optionally substituted heteroarylalkyl);
- $-CHO$ ;

- $-\text{OCON}(\text{R}^6)_2$  ;
- $-\text{NR}^3\text{CO}_2\text{R}^6$  ;
- $-\text{NR}^3\text{CON}(\text{R}^6)_2$
- fused ring-forming bridges attached to and connecting adjacent positions of ring I, said bridges having the structures:

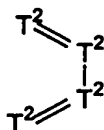
a)



wherein

each  $\text{T}^2$  independently represents N, CH, or  $\text{CG}^4$ ; $\text{T}^3$  represents S, O,  $\text{CR}^4\text{G}^4$ ,  $\text{C}(\text{R}^4)_2$ , or  $\text{NR}^3$ ; andbinding to ring J is achieved via terminal atoms  $\text{T}^2$  and  $\text{T}^3$ ;

b)



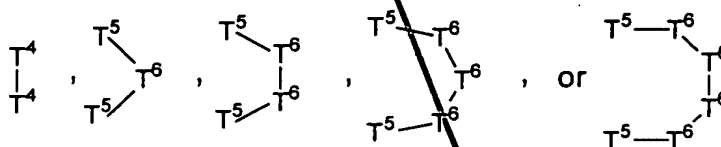
wherein

each  $\text{T}^2$  independently represents N, CH, or  $\text{CG}^4$ ;with the proviso that a maximum of two bridge atoms  $\text{T}^2$  may be N ;

and

binding to ring J is achieved via terminal atoms  $\text{T}^2$ ; and

c).



wherein

each  $\text{T}^4$ ,  $\text{T}^5$ , and  $\text{T}^6$  independently represents O, S,  $\text{CR}^4\text{G}^4$ ,  $\text{C}(\text{R}^4)_2$ , or  $\text{NR}^3$ ; andbinding to ring J is achieved via terminal atoms  $\text{T}^4$  or  $\text{T}^5$  ;

with the provisos that:

i) when one  $\text{T}^4$  is O, S, or  $\text{NR}^3$ , the other  $\text{T}^4$  is  $\text{CR}^4\text{G}^4$  or  $\text{C}(\text{R}^4)_2$  ;ii) a bridge comprising  $\text{T}^5$  and  $\text{T}^6$  atoms may contain a maximum of two heteroatoms O, S, or N; and



iii) in a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms, when one T<sup>5</sup> group and one T<sup>6</sup> group are O atoms, or two T<sup>6</sup> groups are O atoms, said O atoms are separated by at least one carbon atom;

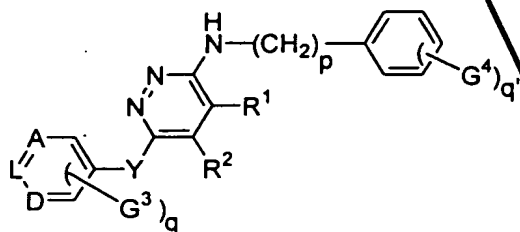
5 and with the further provisos that:

- in G<sup>1</sup>, G<sup>2</sup>, G<sup>3</sup>, and G<sup>4</sup>, when two groups R<sup>6</sup> are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR<sup>3</sup> to form a N-containing heterocycle of 5 - 7 ring atoms; and

10 - when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, -CO<sub>2</sub>R<sup>3</sup>, -CHO, -CH<sub>2</sub>OR<sup>3</sup>, -OCO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, -OCO N(R<sup>6</sup>)<sub>2</sub>, -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>, nitro, amidino, guanidino, mercapto, sulfo, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

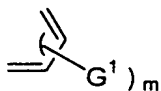
20 2. A compound having the generalized structural formula



wherein

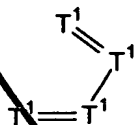
R<sup>1</sup> and R<sup>2</sup> :

i) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms; or

ii) together form a bridge of structure



wherein one of the ring members  $T^1$  is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1 – 2; and

$G^1$  is a substituent independently selected from the group consisting of

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;
- halogen;
- alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- $-OR^6$ ;
- $-SR^6$ ;
- $-S(O)R^6$ ;
- $-S(O)_2R^6$ ;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- $-OCOR^6$ ;
- $-COR^6$ ;
- $-CO_2R^6$ ;

Sub  
A1

10

15

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

20

- $-(\text{CH}_2)_n-\text{S}(\text{O})_p-(5\text{-membered heteroaryl})-(\text{CH}_2)_s-$ ;
- $-(\text{CH}_2)_n-\text{C}(\text{G}^2)(\text{H})-(\text{CH}_2)_s-$ ;

$n$  and  $s$  are each independently 0 or 1; and

G<sup>2</sup> is selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, and -CH<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub>;

- $-\text{O}-\text{CH}_2-$  ;
- $-\text{S}(\text{O})-$  ;
- $-\text{S}(\text{O})_2-$  ;
- $-\text{SCH}_2-$  ;
- $-\text{S}(\text{O})\text{CH}_2-$  ;
- $-\text{S}(\text{O})_2\text{CH}_2-$  ;

- $-\text{CH}_2\text{S}(\text{O})-$ ; and
- $-\text{CH}_2\text{S}(\text{O})_2-$

A and D independently represent N or CH;

5

L represents N or CH;

with the provisos that

- a) the total number of N atoms in the ring containing A, D, and L is 1 or 2; and
- b) when L represents CH, at least one of A and D is an N atom;

10

q is 0, 1, or 2;

$G^3$  is selected from the group consisting of

15

- lower alkyl;
- $-\text{NR}^3\text{COR}^6$ ;
- $-\text{OR}^6$ ;
- $-\text{SR}^6$ ;
- $-\text{S}(\text{O})\text{R}^6$ ;
- $-\text{S}(\text{O})_2\text{R}^6$ ;
- $-\text{CO}_2\text{R}^6$ ;
- $-\text{CON}(\text{R}^6)_2$ ;
- $-\text{S}(\text{O})_2\text{N}(\text{R}^6)_2$ ;
- $-\text{CN}$ ;

20

- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroaryl})$ ;
- optionally substituted heteroarylalkyloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroarylalkyl})$ ;

25

30

$q'$  represents the number of substituents  $G^4$  on the phenyl ring and is 0, 1, 2, or 3;  
and

Sub  
A1

000780" 6T59E960

C<sup>4</sup> moieties are selected from the group consisting of

- -N(R<sup>6</sup>)<sub>2</sub>;
- -NR<sup>3</sup>COR<sup>6</sup>;
- halogen;
- alkyl;
- halogen-substituted alkyl;
- hydroxy-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxy-carbonyl-substituted alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxy-carbonyl-substituted alkylamino;
- phenyl-lower alkoxy-carbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- -NO<sub>2</sub>;
- -CN;

Sub  
A1

000T80" 6T59E960

- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p$ (optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p$ (optionally substituted heteroarylalkyl);
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

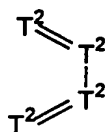
a)



wherein

each  $T^2$  independently represents N, CH, or  $CG^4$ ; $T^3$  represents S, O,  $CHG^4$ ,  $CH_2$ , or  $NR^3$ ; andbinding to the phenyl ring is achieved via terminal atoms  $T^2$  and  $T^3$ ;

b)



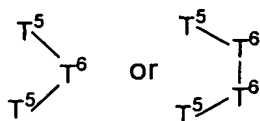
wherein

each  $T^2$  independently represents N, CH, or  $CG^4$ ;with the proviso that a maximum of two bridge atoms  $T^2$  may be N ;

and

binding to the phenyl ring is achieved via terminal atoms  $T^2$ ; and

c)



wherein

each  $T^5$ , and  $T^6$  independently represents O, S,  $CHG^4$ ,  $CH_2$ , or  $NR^3$ ;

and

binding to the phenyl ring is achieved via terminal atoms  $T^5$  ;

with the provisos that:

- i) a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms may contain a maximum of two heteroatoms O, S, or N; and
- ii) in a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms, when one T<sup>5</sup> group and one T<sup>6</sup> group are O atoms, or two T<sup>6</sup> groups are O atoms, said O atoms are separated by at least one carbon atom;

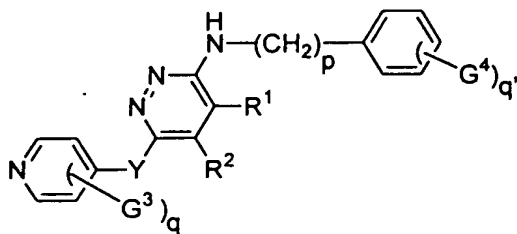
and with the further provisos that:

- in G<sup>1</sup>, G<sup>2</sup>, G<sup>3</sup>, and G<sup>4</sup>, when two groups R<sup>6</sup> are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR<sup>3</sup> to form a N-containing heterocycle of 5 - 7 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, -CO<sub>2</sub>R<sup>3</sup>, -CH<sub>2</sub>OR<sup>3</sup>, -OCO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, -OCO N(R<sup>6</sup>)<sub>2</sub>, -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>, nitro, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

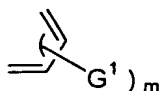
3. A compound having the generalized structural formula



wherein

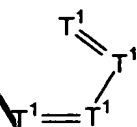
R<sup>1</sup> and R<sup>2</sup> :

- i) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms, and any group G<sup>1</sup> is located on a non-terminal atom of the bridge; or

iv)



wi

w

m

G<sup>1</sup>

- 

R<sup>2</sup> $R^6$ 

- 

p

**Y**

-



- -S(O)- ; and
- -S(O)<sub>2</sub>- ;

q is 0 or 1;

5

G<sup>3</sup> is selected from the group consisting of

- lower alkyl;
- -NR<sup>3</sup>COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub> ;
- -S(O)<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub> ;

10

q' represents the number of substituents G<sup>4</sup> on the phenyl ring and is 0, 1, 2, or 3;  
and

15

G<sup>4</sup> moieties are selected from the group consisting of

- -N(R<sup>6</sup>)<sub>2</sub> ;
- halogen;
- lower alkyl;
- halogen-substituted lower alkyl;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub> ;
- -CH<sub>2</sub>OR<sup>3</sup>;
- -NO<sub>2</sub> ;

20

25

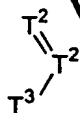
30

000780" 6T59E960

Sub  
A1

- -CN;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

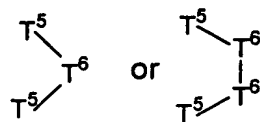
a)



wherein

each T<sup>2</sup> independently represents N, CH, or CG<sup>4</sup>;T<sup>3</sup> represents S, O, CHG<sup>4</sup>, CH<sub>2</sub>, or NR<sup>3</sup>; andbinding to the phenyl ring is achieved via terminal atoms T<sup>2</sup> and T<sup>3</sup>;

b)



wherein

each T<sup>5</sup>, and T<sup>6</sup> independently represents O, S, CHG<sup>4</sup>, CH<sub>2</sub>, or NR<sup>3</sup>;

and

binding to the phenyl ring is achieved via terminal atoms T<sup>5</sup>;

with the provisos that:

- a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms may contain a maximum of two heteroatoms O, S, or N; and
- in a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms, when one T<sup>5</sup> group and one T<sup>6</sup> group are O atoms, or two T<sup>6</sup> groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in  $G^1$ ,  $G^2$ ,  $G^3$ , and  $G^4$ , when two groups  $R^6$  are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or  $NR^3$  to form a N-containing heterocycle of 5-6 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio,  $-CO_2R^3$ ,  $-CON(R^6)_2$ , nitro, and cyano;

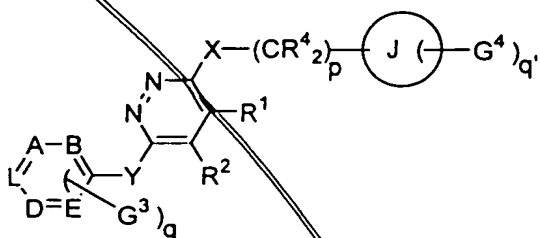
or a pharmaceutically acceptable salt or prodrug thereof.

4. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

5. A method of treating a mammal having a condition characterized by abnormal angiogenesis or hyperpermeability processes, comprising administering to said mammal an amount of a compound of claim 1 which is effective to treat said condition.

6. The method of claim 5, wherein said condition is tumor growth; retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, and age-related macular degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.

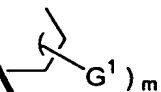
7. A compound having the generalized structural formula



wherein

$R^1$  and  $R^2$  :

- i) independently represent H or lower alkyl;
- ii) together form a bridge of structure



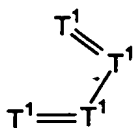
wherein binding is achieved via the terminal carbon atoms;

- iii) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms; or

- iv) together form a bridge of structure



wherein one or two ring members  $T^1$  are N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

$m$  is 0 or an integer 1 – 4; and

$G^1$  is a substituent independently selected from the group consisting of

- $-\text{N}(\text{R}^6)_2$  ;
- $-\text{NR}^3\text{COR}^6$  ;
- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;

- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxy-carbonyl-substituted alkyl;
- phenyl lower alkoxy-carbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxy-carbonyl-substituted alkylamino;
- phenyl-lower alkoxy-carbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- -NO<sub>2</sub>;
- -CN;
- amidino;

5

10

15

20

25

30

- guanidino;
- sulfo;
- -B(OH)<sub>2</sub> ;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- -OCO<sub>2</sub>R<sup>3</sup>;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- -CHO;
- -OCON(R<sup>6</sup>)<sub>2</sub> ;
- -NR<sup>3</sup>CO<sub>2</sub>R<sup>6</sup> ;
- -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>

R<sup>3</sup> is H or lower alkyl;

R<sup>6</sup> is independently selected from the group consisting of

- H;
- alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

R<sup>4</sup> is H, halogen, or lower alkyl;

p is 0, 1, or 2;

X is selected from the group consisting of O, S, and NH;

Sub  
A3

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH or OAcyl;
- -CH<sub>2</sub>-O- ;
- -CH<sub>2</sub>-S- ;
- -CH<sub>2</sub>-NH- ;
- -O- ;
- -S- ;
- -NH- ;
- -(CR<sup>4</sup>)<sub>n</sub>-S(O)<sub>p</sub>-(5-membered heteroaryl)-(CR<sup>4</sup>)<sub>s</sub>-;
- -(CR<sup>4</sup>)<sub>n</sub>-C(G<sup>2</sup>)(R<sup>4</sup>)-(CR<sup>4</sup>)<sub>s</sub>- ;

wherein

n and s are each independently 0 or an integer of 1 – 2; and

G<sup>2</sup> is selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, and

-CH<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub> ;

- -O-CH<sub>2</sub>- ;
- -S(O)- ;
- -S(O)<sub>2</sub>- ;
- -SCH<sub>2</sub>- ;
- -S(O)CH<sub>2</sub>- ;
- -S(O)<sub>2</sub>CH<sub>2</sub>- ;
- -CH<sub>2</sub>S(O)- ; and
- -CH<sub>2</sub>S(O)<sub>2</sub>-

A and D independently represent N or CH;

B and E independently represent N or CH;

L represents N or CH;

with the provisos that

a) the total number of N atoms in the ring containing A, B, D, E, and L is 1, 2, or 3; and

b) when L represents CH, at least one of A and D is an N atom;

q is 0, 1, or 2;

$G^3$  is selected from the group consisting of

- $-NR^3COR^6$ ;
- carboxy-substituted alkyl;
- lower alkoxy-carbonyl-substituted alkyl;
- $-OR^6$ ;
- $-SR^6$ ;
- $-S(O)R^6$ ;
- $-S(O)_2R^6$ ;
- $-OCOR^6$ ;
- $-COR^6$ ;
- $-CO_2R^6$ ;
- $-CH_2OR^3$ ;
- $-CON(R^6)_2$ ;
- $-S(O)_2N(R^6)_2$ ;
- $-NO_2$ ;
- $-CN$ ;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p(\text{optionally substituted heteroaryl})$ ;
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p(\text{optionally substituted heteroarylalkyl})$ ;
- $-OCON(R^6)_2$ ;
- $-NR^3CO_2R^6$ ;
- $-NR^3CON(R^6)_2$ ;

J is a ring selected from the group consisting of

- aryl;



Sub  
A3

- 5

$q'$  represents the number of substituents  $G^4$  on ring J and is 0, 1, 2, 3, 4, or 5, and  $G^4$  moieties are selected from the group consisting of

- 15

- 20

- 25

- 30

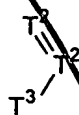
5<sup>ub</sup>  
A3

000T80"6T59E960

- phenyl-lower alkoxy carbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- -NO<sub>2</sub>;
- -CN;
- amidino;
- guanidino;
- sulfo;
- -B(OH)<sub>2</sub>;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- -OCO<sub>2</sub>R<sup>3</sup>;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- -CHO;
- -OCON(R<sup>6</sup>)<sub>2</sub>;

- $-\text{NR}^3\text{CO}_2\text{R}^6$ ;
- $-\text{NR}^3\text{CON}(\text{R}^6)_2$
- fused ring-forming bridges attached to and connecting adjacent positions of ring J, said bridges having the structures:

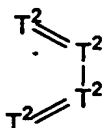
a)



wherein

each  $\text{T}^2$  independently represents N, CH, or  $\text{CG}^4$ ; $\text{T}^3$  represents S, O,  $\text{CR}^4\text{G}^4$ ,  $\text{C}(\text{R}^4)_2$ , or  $\text{NR}^3$ ; andbinding to ring J is achieved via terminal atoms  $\text{T}^2$  and  $\text{T}^3$ ;

b)



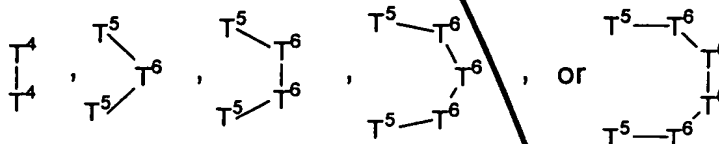
wherein

each  $\text{T}^2$  independently represents N, CH, or  $\text{CG}^4$ ;with the proviso that a maximum of two bridge atoms  $\text{T}^2$  may be N ;

and

binding to ring J is achieved via terminal atoms  $\text{T}^2$ ; and

c)



wherein

each  $\text{T}^4$ ,  $\text{T}^5$ , and  $\text{T}^6$  independently represents O, S,  $\text{CR}^4\text{G}^4$ ,  $\text{C}(\text{R}^4)_2$ , or  $\text{NR}^3$ ; andbinding to ring J is achieved via terminal atoms  $\text{T}^4$  or  $\text{T}^5$  ;

with the provisos that:

i) when one  $\text{T}^4$  is O, S, or  $\text{NR}^3$ , the other  $\text{T}^4$  is  $\text{CR}^4\text{G}^4$  or  $\text{C}(\text{R}^4)_2$  ;ii) a bridge comprising  $\text{T}^5$  and  $\text{T}^6$  atoms may contain a maximum of two heteroatoms O, S, or N; and

iii) in a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms, when one T<sup>5</sup> group and one T<sup>6</sup> group are O atoms, or two T<sup>6</sup> groups are O atoms, said O atoms are separated by at least one carbon atom;

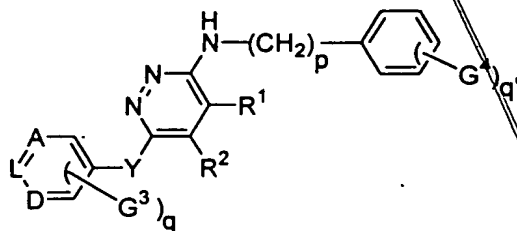
5 and with the further provisos that:

- in G<sup>1</sup>, G<sup>2</sup>, G<sup>3</sup>, and G<sup>4</sup>, when two groups R<sup>6</sup> are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR<sup>3</sup> to form a N-containing heterocycle of 5 - 7 ring atoms; and

10 - when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, -CO<sub>2</sub>R<sup>3</sup>, -CHO, -CH<sub>2</sub>OR<sup>3</sup>, -OCO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, -OCO N(R<sup>6</sup>)<sub>2</sub>, -NR<sup>3</sup>CON(R<sup>6</sup>)<sub>2</sub>, nitro, amidino, guanidino, mercapto, sulfo, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

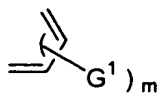
20 8. A compound having the generalized structural formula



wherein

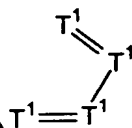
R<sup>1</sup> and R<sup>2</sup> :

i) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms; or

ii) together form a bridge of structure



wherein one of the ring members  $T^1$  is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1 – 2; and

$G^1$  is a substituent independently selected from the group consisting of

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;
- halogen;
- alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxy-carbonyl-substituted alkylamino;
- $-OR^6$ ;
- $-SR^6$ ;
- $-S(O)R^6$ ;
- $-S(O)_2R^6$ ;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- $-OCOR^6$ ;
- $-COR^6$ ;
- $-CO_2R^6$ ;

[illegible]

5

- 10

$R^6$  is independently selected from the group consisting of

- 15

20

- lower alkylene, optionally substituted by OH or OAcyl;
- $-\text{CH}_2-\text{O}-$  ;
- $-\text{CH}_2-\text{S}-$  ;
- $-\text{CH}_2-\text{NH}-$  ;
- $-\text{O}-$  ;
- $-\text{S}-$  ;
- $-\text{NH}-$  ;
- $-(\text{CH}_2)_n-\text{S}(\text{O})_p-(5\text{-membered heteroaryl})-(\text{CH}_2)_s-$  ;
- $-(\text{CH}_2)_n-\text{C}(\text{G}^2)(\text{H})-(\text{CH}_2)_s-$  ;

25

30

$n$  and  $s$  are each independently 0 or 1; and

Sub  
A3

5

10

20

25

30

- optionally substituted heteroarylalkyl;

89

L represents N or CH;

15

b) when L represents CH, at least one of A and D is an N atom;

20

- $-NR^3COR^6$ ;

- $-SR^6$ ;

- $-S(O)R^6$ ;

- $-S(O)_2R^6$ ;

- $-\text{CO}_2\text{R}^6$ ;

- $-\text{CON}(\text{R}^6)_2$  ;

- $-S(O)_2N(R^6)_2$  ;

- -CN;

- optionally substituted aryl;

- optionally substituted heteroaryl;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroarylloxy;
- $-S(O)_p(\text{optionally substituted heteroaryl})$ ;
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p(\text{optionally substituted heteroarylalkyl})$ ;

5

$q'$  represents the number of substituents  $G^4$  on the phenyl ring and is 0, 1, 2, or 3;  
and

$G^4$  moieties are selected from the group consisting of

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;
- halogen;
- alkyl;
- halogen-substituted alkyl;
- hydroxy-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxy-carbonyl-substituted alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxy-carbonyl-substituted alkylamino;
- phenyl-lower alkoxy-carbonyl-substituted alkylamino;
- $-OR^6$ ;
- $-SR^6$ ;
- $-S(O)R^6$ ;
- $-S(O)_2R^6$ ;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- $-OCOR^6$ ;

10

15

20

25

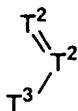
30

Sub  
K3



- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -CH<sub>2</sub>OR<sup>3</sup>;
- -NO<sub>2</sub>;
- -CN;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

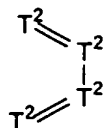
a)



wherein

each T<sup>2</sup> independently represents N, CH, or CG<sup>4</sup>;T<sup>3</sup> represents S, O, CHG<sup>4</sup>, C(H)<sub>2</sub>, or NR<sup>3</sup>; andbinding to the phenyl ring is achieved via terminal atoms T<sup>2</sup> and T<sup>3</sup>;

b)



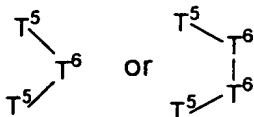
wherein

each T<sup>2</sup> independently represents N, CH, or CG<sup>4</sup>;with the proviso that a maximum of two bridge atoms T<sup>2</sup> may be N ;

and

binding to the phenyl ring is achieved via terminal atoms T<sup>2</sup>; and

c)

Sub  
A3

000780" 6T59E960

wherein

each  $T^5$ , and  $T^6$  independently represents O, S,  $CHG^4$ ,  $C(H)_2$ , or  $NR^3$ ;

and

binding to the phenyl ring is achieved via terminal atoms  $T^5$ ;

with the provisos that:

- i) a bridge comprising  $T^5$  and  $T^6$  atoms may contain a maximum of two heteroatoms O, S, or N; and
- ii) in a bridge comprising  $T^5$  and  $T^6$  atoms, when one  $T^5$  group and one  $T^6$  group are O atoms, or two  $T^6$  groups are O atoms, said O atoms are separated by at least one carbon atom;

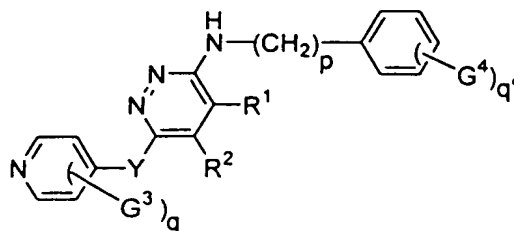
and with the further provisos that:

- in  $G^1$ ,  $G^2$ ,  $G^3$ , and  $G^4$  when two groups  $R^6$  are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or  $NR^3$  to form a N-containing heterocycle of 5 - 7 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy,  $-CO_2R^3$ ,  $-CH_2OR^3$ ,  $-OCO_2R^3$ ,  $-CON(R^6)_2$ ,  $-OCO N(R^6)_2$ ,  $-NR^3CON(R^6)_2$ , nitro, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

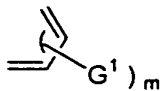
9. A compound having the generalized structural formula



wherein

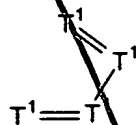
$R^1$  and  $R^2$  :

i) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms, and any group  $G^1$  is located on a non-terminal atom of the bridge; or

ii) together form a bridge of structure



wherein one of the ring members  $T^1$  is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

$m$  is 0 or an integer 1 – 2; and

$G^1$  is a substituent independently selected from the group consisting of

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;
- halogen;
- $-OR^6$  wherein  $R^6$  represents lower alkyl;
- $-NO_2$ ;
- optionally substituted heteroaryloxy;
- optionally substituted heteroarylalkyloxy;

$R^3$  is H or lower alkyl;

$R^6$  is independently selected from the group consisting of

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

p is 0 or 1;

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH;
- $-\text{CH}_2-\text{O}-$ ;
- $-\text{S}-$ ;
- $-\text{NH}-$ ;
- $-\text{S}(\text{O})_p-(5\text{-membered heteroaryl})-$ ;
- $-\text{C}(\text{CN})(\text{H})-$ ;
- $-\text{O}-\text{CH}_2-$ ;
- $-\text{S}(\text{O})-$ ; and
- $-\text{S}(\text{O})_2-$ ;

q is 0 or 1;

$G^3$  is selected from the group consisting of

- $-\text{NR}^3\text{COR}^6$ ;
- $-\text{CO}_2\text{R}^6$ ;
- $-\text{CON}(\text{R}^6)_2$ ;
- $-\text{S}(\text{O})_2\text{N}(\text{R}^6)_2$ ;

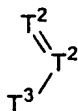
$q'$  represents the number of substituents  $G^4$  on the phenyl ring and is 0, 1, 2, or 3;  
and

$G^4$  moieties are selected from the group consisting of

- $-\text{N}(\text{R}^6)_2$ ;
- halogen;
- lower alkyl;
- halogen-substituted lower alkyl;
- $-\text{OR}^6$ ;
- $-\text{SR}^6$ ;
- $-\text{S}(\text{O})\text{R}^6$ ;
- $-\text{S}(\text{O})_2\text{R}^6$ ;

- 5
- halogenated lower alkoxy;
  - halogenated lower alkylthio;
  - halogenated lower alkylsulfonyl;
  - $-\text{OCOR}^6$ ;
  - $-\text{COR}^6$ ;
  - $-\text{CO}_2\text{R}^6$ ;
  - $-\text{CON}(\text{R}^6)_2$ ;
  - $-\text{CH}_2\text{OR}^6$ ;
  - $-\text{NO}_2$ ;
  - $-\text{CN}$ ;
  - optionally substituted heteroarylalkyl;
  - optionally substituted heteroaryloxy;
  - $-\text{S}(\text{O})_p(\text{optionally substituted heteroaryl})$ ;
  - optionally substituted heteroarylalkyloxy;
  - $-\text{S}(\text{O})_p(\text{optionally substituted heteroarylalkyl})$ ;
  - fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

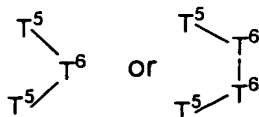
a)



wherein

each  $\text{T}^2$  independently represents N, CH, or  $\text{CG}^4$ ; $\text{T}^3$  represents S, O,  $\text{CHG}^4$ ,  $\text{CH}_2$ , or  $\text{NR}^3$ ; andbinding to the phenyl ring is achieved via terminal atoms  $\text{T}^2$  and  $\text{T}^3$ ;

b)



wherein

each  $\text{T}^5$ , and  $\text{T}^6$  independently represents O, S,  $\text{CHG}^4$ ,  $\text{CH}_2$ , or  $\text{NR}^3$ ;

and

binding to the phenyl ring is achieved via terminal atoms  $\text{T}^5$ ;

with the provisos that:

- i) a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms may contain a maximum of two heteroatoms O, S, or N; and
- ii) in a bridge comprising T<sup>5</sup> and T<sup>6</sup> atoms, when one T<sup>5</sup> group and one T<sup>6</sup> group are O atoms, or two T<sup>6</sup> groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

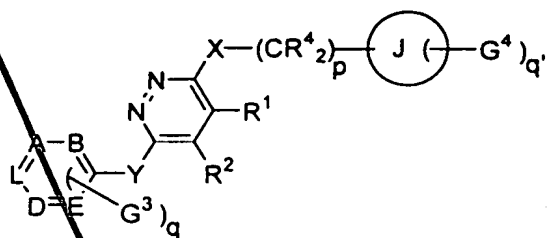
- in G<sup>1</sup>, G<sup>2</sup>, G<sup>3</sup>, and G<sup>4</sup>, when two groups R<sup>6</sup> are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR<sup>3</sup> to form a N-containing heterocycle of 5 - 6 ring atoms; and
  - when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, -CO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, nitro, and cyano;
- or a pharmaceutically acceptable salt or prodrug thereof.

10. A pharmaceutical composition comprising a compound of claim 7 and a pharmaceutically acceptable carrier.

11. A method of treating a mammal having a condition characterized by abnormal angiogenesis or hyperpermeability processes, comprising administering to said mammal an amount of a compound of claim 7 which is effective to treat said condition.

12. The method of claim 11, wherein said condition is tumor growth; retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, and age-related macular degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.

13. A compound having the generalized structural formula



wherein

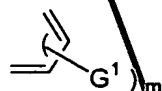
$R^1$  and  $R^2$  :

- i) independently represent H or lower alkyl;
- ii) together form a bridge of structure



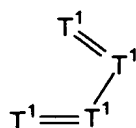
wherein binding is achieved via the terminal carbon atoms;

- iii) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms; or

- iv) together form a bridge of structure



wherein one or two ring members  $T^1$  are N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

$m$  is 0 or an integer 1 – 4; and

$G^1$  is a substituent independently selected from the group consisting of

- $-N(R^6)_2$ ;
- $-NR^3COR^6$ ;
- halogen;
- alkyl;
- cycloalkyl;

- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- phenyl lower alkoxycarbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;

Sub  
AS

000T80"6T59E960



- $-\text{CO}_2\text{R}^6$ ;
- $-\text{CON}(\text{R}^6)_2$ ;
- $-\text{CH}_2\text{OR}^3$ ;
- $-\text{NO}_2$ ;
- $-\text{CN}$ ;
- amidino;
- guanidino;
- sulfo;
- $-\text{B}(\text{OH})_2$ ;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- $-\text{OCO}_2\text{R}^3$ ;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroaryl})$ ;
- optionally substituted heteroarylalkyloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroarylalkyl})$ ;
- $-\text{CHO}$ ;
- $-\text{OCON}(\text{R}^6)_2$ ;
- $-\text{NR}^3\text{CO}_2\text{R}^6$ ;
- $-\text{NR}^3\text{CON}(\text{R}^6)_2$

25  $\text{R}^3$  is H or lower alkyl;

$\text{R}^6$  is independently selected from the group consisting of

- H;
- alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

~~p is 0, 1, or 2;~~

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH or OAcyl;
- $-\text{CH}_2-\text{O}-$ ;
- $-\text{CH}_2-\text{S}-$ ;
- $-\text{CH}_2-\text{NH}-$ ;
- $-\text{O}-$ ;
- $-\text{S}-$ ;
- $-\text{NH}-$ ;
- $-(\text{CR}^4_2)_n-\text{S}(\text{O})_p-(5\text{-membered heteroaryl})-(\text{CR}^4_2)_s-$ ;
- $-(\text{CR}^4_2)_n-\text{C}(\text{G}^2)(\text{R}^4)-(\text{CR}^4_2)_s-$ ;

$n$  and  $s$  are each independently 0 or an integer of  $1 - 2$ ; and

G<sup>2</sup> is selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>6</sup>)<sub>2</sub>, and

$$-\text{CH}_2\text{N}(\text{R}^6)_2 ;$$

- $-\text{O}-\text{CH}_2-$  ;
- $-\text{S}(\text{O})-$  ;
- $-\text{S}(\text{O})_2-$  ;
- $-\text{SCH}_2-$  ;
- $-\text{S}(\text{O})\text{CH}_2-$  ;
- $-\text{S}(\text{O})_2\text{CH}_2-$  ;
- $-\text{CH}_2\text{S}(\text{O})-$  ; and
- $-\text{CH}_2\text{S}(\text{O})_2-$

30 A and D independently represent N or CH;  
B and E independently represent N or CH;  
L represents N or CH;

100

b) when L represents CH, at least one of A and D is an N atom;

$G^3$  is selected from the group consisting of

- 10

15

20

25

30

- $-\text{OCON}(\text{R}^6)_2$ ;
- $-\text{NR}^3\text{CO}_2\text{R}^6$ ;
- $-\text{NR}^3\text{CON}(\text{R}^6)_2$ ;

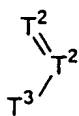
5 J is a ring selected from the group consisting of

- aryl;
- pyridyl; and
- cycloalkyl;

10  $q'$  represents the number of substituents  $\text{G}^4$  on ring J and is 0, 1, 2, 3, 4, or 5, and  $\text{G}^4$  moieties are selected from the group consisting of

- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroaryl})$ ;
- 15 • optionally substituted heteroarylalkyloxy;
- $-\text{S}(\text{O})_p(\text{optionally substituted heteroarylalkyl})$ ;
- $-\text{CHO}$ ;
- $-\text{OCON}(\text{R}^6)_2$ ;
- $-\text{NR}^3\text{CO}_2\text{R}^6$ ;
- 20 •  $-\text{NR}^3\text{CON}(\text{R}^6)_2$
- fused ring-forming bridges attached to and connecting adjacent positions of ring J, said bridges having the structures:

a)



25

wherein

each  $\text{T}^2$  independently represents N,  $\text{CH}$ , or  $\text{CG}^4$ ;

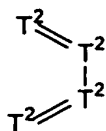
$\text{T}^3$  represents S, O,  $\text{CR}^4\text{G}^4$ ,  $\text{C}(\text{R}^4)_2$ , or  $\text{NR}^3$ ; and

binding to ring J is achieved via terminal atoms  $\text{T}^2$  and  $\text{T}^3$ ;

Sub  
AS

000000-000000-000000

b)



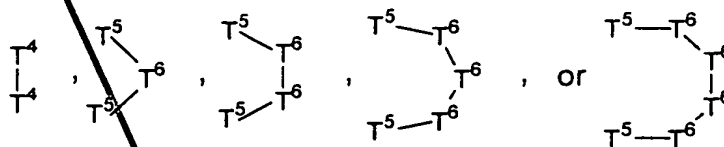
wherein

each  $T^2$  independently represents N, CH, or  $CG^4$ ;with the proviso that a maximum of two bridge atoms  $T^2$  may be N ;

and

binding to ring J is achieved via terminal atoms  $T^2$ ; and

c)



wherein

each  $T^4$ ,  $T^5$ , and  $T^6$  independently represents O, S,  $CR^4G^4$ ,  $C(R^4)_2$ , or  $NR^3$ ; andbinding to ring J is achieved via terminal atoms  $T^4$  or  $T^5$  ;

with the provisos that:

- i) when one  $T^4$  is O, S, or  $NR^3$ , the other  $T^4$  is  $CR^4G^4$  or  $C(R^4)_2$  ;
- ii) a bridge comprising  $T^5$  and  $T^6$  atoms may contain a maximum of two heteroatoms O, S, or N; and
- iii) in a bridge comprising  $T^5$  and  $T^6$  atoms, when one  $T^5$  is O, the other  $T^5$  is S,  $CR^4G^4$ ,  $C(R^4)_2$  or  $NR^3$  ;
- iv) in a bridge comprising  $T^5$  and  $T^6$  atoms, when one  $T^5$  group and one  $T^6$  group are O atoms, or two  $T^6$  groups are O atoms, said O atoms are separated by at least one carbon atom;

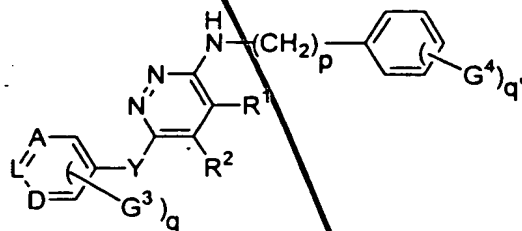
and with the further provisos that:

- in  $G^1$ ,  $G^2$ ,  $G^3$ , and  $G^4$ , when two groups  $R^6$  are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or  $NR^3$  to form a N-containing heterocycle of 5 - 7 ring atoms; and

when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy,  $-\text{CO}_2\text{R}^3$ ,  $-\text{CHO}$ ,  $-\text{CH}_2\text{OR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{CON}(\text{R}^6)_2$ ,  $-\text{OCO N}(\text{R}^6)_2$ ,  $-\text{NR}^3\text{CON}(\text{R}^6)_2$ , nitro, amidino, guanidino, mercapto, sulfo, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

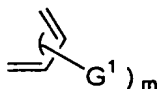
14. A compound having the generalized structural formula



wherein

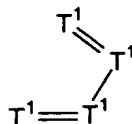
$\text{R}^1$  and  $\text{R}^2$ :

i) together form a bridge of structure



wherein binding is achieved via the terminal carbon atoms; or

ii) together form a bridge of structure



wherein one of the ring members  $\text{T}^1$  is N and the others are CH, and binding is achieved via the terminal atoms; and

wherein

$m$  is 0 or an integer 1 – 2; and

$\text{G}^1$  is a substituent independently selected from the group consisting of

- $-\text{N}(\text{R}^6)_2$ ;

Sub  
AS

5

10

15

20

25

30

- -NR<sup>3</sup>COR<sup>6</sup> ;
- halogen;
- alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxy-carbonyl-substituted alkylamino;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR<sup>6</sup>;
- -COR<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub> ;
- -NO<sub>2</sub> ;
- -CN;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);

$R^3$  is H or lower alkyl;

$R^6$  is independently selected from the group consisting of

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

5

p is 0 or 1;

Y is selected from the group consisting of

10

- lower alkylene, optionally substituted by OH or OAcyl;
- $-\text{CH}_2-\text{O}-$ ;
- $-\text{CH}_2-\text{S}-$ ;
- $-\text{CH}_2-\text{NH}-$ ;
- $-\text{O}-$ ;
- $-\text{S}-$ ;
- $-\text{NH}-$ ;
- $-(\text{CH}_2)_n-\text{S}(\text{O})_p-(5\text{-membered heteroaryl})-(\text{CH}_2)_s-$ ;
- $-(\text{CH}_2)_n-\text{C}(\text{G}^2)(\text{H})-(\text{CH}_2)_s-$ ;

15

wherein

20

n and s are each independently 0 or 1; and

$\text{G}^2$  is selected from the group consisting of  $-\text{CN}$ ,  $-\text{CO}_2\text{R}^3$ ,  $-\text{CON}(\text{R}^6)_2$ , and

$-\text{CH}_2\text{N}(\text{R}^6)_2$ ;

25

- $-\text{O}-\text{CH}_2-$ ;
- $-\text{S}(\text{O})-$ ;
- $-\text{S}(\text{O})_2-$ ;
- $-\text{SCH}_2-$ ;
- $-\text{S}(\text{O})\text{CH}_2-$ ;
- $-\text{S}(\text{O})_2\text{CH}_2-$ ;
- $-\text{CH}_2\text{S}(\text{O})-$ ; and
- $-\text{CH}_2\text{S}(\text{O})_2-$

30

A and D independently represent N or CH;

Sub  
AS

000000-000000-000000



L represents N or CH;

with the provisos that

- a) the total number of N atoms in the ring containing A, D, and L is 1 or 2; and
- b) when L represents CH, at least one of A and D is an N atom;

5

q is 0, 1, or 2;

G<sup>3</sup> is selected from the group consisting of

- lower alkyl;
- -NR<sup>3</sup>COR<sup>6</sup>;
- -OR<sup>6</sup>;
- -SR<sup>6</sup>;
- -S(O)R<sup>6</sup>;
- -S(O)<sub>2</sub>R<sup>6</sup>;
- -CO<sub>2</sub>R<sup>6</sup>;
- -CON(R<sup>6</sup>)<sub>2</sub>;
- -S(O)<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub>;
- -CN;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);

10

15

20

25

q' represents the number of substituents G<sup>4</sup> on the phenyl ring and is 0, 1, 2, or 3;  
and

G<sup>4</sup> moieties are selected from the group consisting of

30

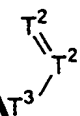
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);

Sub  
AS

000130" 5753E950

- optionally substituted heteroarylalkyloxy;
- $\text{S}(\text{O})_p(\text{optionally substituted heteroarylalkyl})$ ;
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

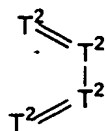
a)



wherein

each  $\text{T}^2$  independently represents N, CH, or  $\text{CG}^4$ ; $\text{T}^3$  represents S, O,  $\text{CHG}^4$ ,  $\text{C}(\text{H})_2$ , or  $\text{NR}^3$ ; andbinding to the phenyl ring is achieved via terminal atoms  $\text{T}^2$  and  $\text{T}^3$ ;

b)



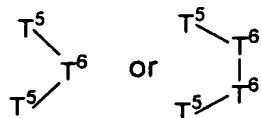
wherein

each  $\text{T}^2$  independently represents N, CH, or  $\text{CG}^4$ ;with the proviso that a maximum of two bridge atoms  $\text{T}^2$  may be N ;

and

binding to the phenyl ring is achieved via terminal atoms  $\text{T}^2$ ; and

c)



wherein

each  $\text{T}^5$ , and  $\text{T}^6$  independently represents O, S,  $\text{CHG}^4$ ,  $\text{CH}_2$ , or  $\text{NR}^3$ ;

and

binding to the phenyl ring is achieved via terminal atoms  $\text{T}^5$  ;

with the provisos that:

- a bridge comprising  $\text{T}^5$  and  $\text{T}^6$  atoms may contain a maximum of two heteroatoms O, S, or N; and
- in a bridge comprising  $\text{T}^5$  and  $\text{T}^6$  atoms, when one  $\text{T}^5$  is O, the other  $\text{T}^5$  is S,  $\text{CHG}^4$ ,  $\text{CH}_2$  or  $\text{NR}^3$  ;

iii) in a bridge comprising  $T^5$  and  $T^6$  atoms, when one  $T^5$  group and one  $T^6$  group are O atoms, or two  $T^6$  groups are O atoms, said O atoms are separated by at least one carbon atom;

5

and with the further provisos that:

- in  $G^1$ ,  $G^2$ ,  $G^3$ , and  $G^4$ , when two groups  $R^6$  are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or  $NR^3$  to form a N-containing heterocycle of 5 - 7 ring atoms; and

10

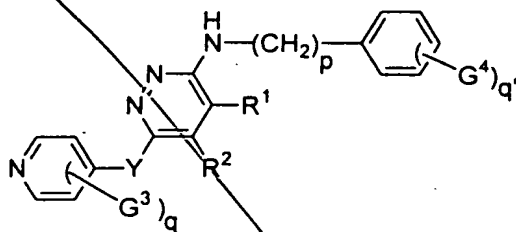
- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy,  $-CO_2R^3$ ,  $-CH_2OR^3$ ,  $-OCO_2R^3$ ,  $-CON(R^6)_2$ ,  $-OCON(R^6)_2$ ,  $-NR^3CON(R^6)_2$ , nitro, and cyano;

15

or a pharmaceutically acceptable salt or prodrug thereof.

20

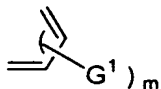
15. A compound having the generalized structural formula



wherein

$R^1$  and  $R^2$ :

i) together form a bridge of structure



25

wherein binding is achieved via the terminal carbon atoms, and any group  $G^1$  is located on a non-terminal atom of the bridge; or

$$\begin{array}{c} T^1 \\ \parallel \\ T^1 \\ / \\ T^1 = T^1 \end{array}$$

wherein

G<sup>1</sup> is a substituent independently selected from the group consisting of

- $R^3$  is H or lower alkyl;

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

Y is selected from the group consisting of

- 110

Sub

- $q$  is 0 or 1;

$G^3$  is selected from the group consisting of

- 15

20

- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)<sub>p</sub>(optionally substituted heteroarylalkyl);

- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

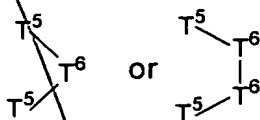
$$\begin{array}{c} T^2 \\ \parallel \\ T^2 \\ / \\ T^3 \end{array}$$

wherein

each  $T^2$  independently represents N, CH, or  $CG^4$ ;

$T^3$  represents S, O,  $CHG^4$ ,  $CH_2$ , or  $NR^3$ ; and  
binding to the phenyl ring is achieved via terminal atoms  $T^2$  and  $T^3$ ;

b)



wherein

each  $T^5$ , and  $T^6$  independently represents O, S,  $CHG^4$ ,  $CH_2$ , or  $NR^3$ ;  
and

binding to the phenyl ring is achieved via terminal atoms  $T^5$ ;  
with the provisos that:

- i) a bridge comprising  $T^5$  and  $T^6$  atoms may contain a maximum of two heteroatoms O, S, or N; and
- ii) in a bridge comprising  $T^5$  and  $T^6$  atoms, when one  $T^5$  is O, the other  $T^5$  is S,  $CR^4G^4$ ,  $C(R^4)_2$  or  $NR^3$ ;
- iii) in a bridge comprising  $T^5$  and  $T^6$  atoms, when one  $T^5$  group and one  $T^6$  group are O atoms, or two  $T^6$  groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in  $G^1$ ,  $G^2$ ,  $G^3$ , and  $G^4$ , when two groups  $R^6$  are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or  $NR^3$  to form a N-containing heterocycle of 5 - 6 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio,  $-CO_2R^3$ ,  $-CON(R^6)_2$ , nitro, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

16. A pharmaceutical composition comprising a compound of claim 13 and a pharmaceutically acceptable carrier.

5

10

15

Sub  
A7

20

25

30

1) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid methylamide dimethanesulfonate;

Sub  
AT

5

10

15

- m) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid amide dihydrochloride;
- n) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid amide dimethanesulfonate;
- o) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic acid amide dihydrochloride;
- p) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic acid amide dimethanesulfonate;
- q) 1-(4-chlorophenylamino)-4-[5-(4-pyridyl)-1H-1,2,4-triazolyl-3-ylthio]phthalazine;
- r) 1-(4-isopropylphenylamino)-4-[5-(4-pyridyl)-1H-1,2,4-triazolyl-3-ylthio]phthalazine
- s) 1-(4-chlorophenylamino)-4-(4-pyridylsulfonyl)phthalazine;
- t) 1-(4-chlorophenylamino)-4-(4-pyridylsulfinyl)phthalazine;
- u) 1-(4-chlorophenylamino)-4-(4-pyridylmethoxy)pyridazine;
- v) 1-(indan-5-ylamino)-4-(4-pyridylcyanomethyl)phthalazine; and
- w) 1-(benzothiazol-6-ylamino)-4-(4-pyridylcyanomethyl)phthalazine;

add  
A8